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Arthritis in idiopathic inflammatory myopathy: clinical features and autoantibody associations

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Arthritis in idiopathic inflammatory myopathy: clinical features and autoantibody associations

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ABSTRACT

Objectives. To determine the prevalence, distribution and clinical manifestations of arthritis in a cohort of patients with idiopathic inflammatory myopathies (IIM). Associations with autoantibody status and HLA genetic background were also explored.

Methods. One hundred and six consecutive patients with IIM treated in a single center were included in this cross-sectional study. History of arthritis, 68/66- tender and swollen joint index, clinical features of IIM, and autoantibody profiles were obtained by clinical examination, personal interview and review of patient's records. High resolution genotyping in HLA-DRB1 and HLA-DQB1 loci was performed in 71 and 73 patients respectively.

Results. Combination of patients' medical history and cross-sectional physical examination revealed that arthritis at any time during the disease course had occurred in 56 patients (53%). It was present at the beginning of the disease in 39 patients (37%) including 23 cases (22%) with arthritis preceding the onset of muscle weakness. On physical examination 29% of patients had at least one swollen joint. The most frequently affected areas were wrists, metacarpophalangeal and proximal interphalangeal joints. Twenty-seven out of the 29 anti-Jo-1 positive patients had arthritis at any time during the course of their illness; prevalence significantly higher compared to patients without the anti-Jo-1 autoantibody ($p < 0.0001$). No association of arthritis with individual HLA alleles was found.

Conclusions. Our data suggest that arthritis is a common feature of myositis. It is frequently present at the onset of disease and it may even precede muscular manifestations of IIM. Most common presentation is a symmetrical, non-erosive polyarthritis affecting particularly wrists, shoulders, and small joints of the hands. We have confirmed a strong association of arthritis with the presence of anti-Jo-1 antibody.

Key words: Idiopathic inflammatory myopathies, Arthritis, Autoantibodies

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INTRODUCTION:

Idiopathic inflammatory myopathies (IIM) represent a group of systemic autoimmune disorders characterized by a non-suppurative inflammation of skeletal muscles as the major manifestation. Distinct subgroups of IIMs with variable clinical and laboratory manifestations are recognized, such as polymyositis (PM), dermatomyositis (DM), juvenile dermatomyositis (JDM), cancer-associated myositis (CAM), immune-mediated necrotizing myopathy (IMNM) and inclusion body myositis (IBM).

Arthritis is commonly seen in patients with IIM, however comprehensive data on its presentation and on manifestations in individual myositis subgroups is scarce (1). Arthritis is particularly frequent in patients with autoantibodies directed against tRNA synthetases as part of the antisynthetase syndrome (2-6), but it is not limited to this subgroup (7, 8). Arthritis and/or arthralgias were reported in 33% of IIM patients in a large multicenter Japanese cohort used for a formulation of new classification criteria, in which arthritis was included (9). Other available information originate from case reports (10-13) or small cohorts selectively defined by the presence of a specific autoantibody or anti-synthetase syndrome (5, 14-16). Arthritis in IIM patients is considered to be less severe and less destructive when compared to the joint involvement in rheumatoid arthritis, but the few available reports provide conflicting results in this aspect (5, 9-16). The degree of reported joint involvement in myositis varies from non-erosive arthritis (12) and subluxing arthropathy (5) to erosive and destructive arthritis (10, 13, 14).

The aim of this study was to provide comprehensive data regarding joint involvement in unselected patients with IIM from a single center. Specifically we determined the prevalence of arthritis in IIM patients; its relation to the course of the muscle disease; characteristics of arthritis with respect to distribution and extent as well as its association with autoantibody profiles and HLA allelic polymorphisms.

METHODS

Patients and Controls

All patients with IIM fulfilling diagnostic criteria seen both at the out- and in-patient departments of the Institute of Rheumatology between January to September 2012 were recruited into the study. The diagnosis of PM and DM was based on the criteria of Bohan and Peter (17, 18), necrotizing myopathy and amyopathic DM were diagnosed using the ENMC criteria (19); and the diagnosis of IBM was established using the Griggs criteria (20). All patients had a muscle biopsy performed during the course of their disease; however, the full description of the findings required for classification according to the ENMC criteria was available for the 76 biopsies performed after 2004 only. Control group for the genetic substudy consisted of 179 healthy subjects. The study was approved by the Ethics committee at the Institute of Rheumatology and all patients signed an informed consent.

Clinical Data

Basic demographic and clinical data including the history of IIM onset, disease course, smoking history and presence of lung involvement (defined as a presence of active alveolitis or fibrotic changes on X-ray or high resolution CT scan; and/or diffusing capacity of the lung for carbon monoxide <70%) were obtained from all patients. Information regarding presence or absence of arthritis in the past and/or at the current time with respect to the onset, localization, and symmetry as well as other features of joint involvement, such as presence of joint deformities, “floppy thumb” was obtained during personal interviews with patients and/or from medical records. Activity of arthritis and the degree of joint involvement were assessed by both patients and physicians using visual analogue scales (VAS). A semi-quantitative scale was used to evaluate the severity of joint involvement as a proportion of total morbidity. History of arthritis was established if the patient during personal interview reported having at least one painful and swollen joint in the past or if the presence of inflammatory arthritis detected by an experienced rheumatologist was recorded in the medical records. Current arthritis was defined as a presence of at least one swollen joint on physical examination using the 68/66-joint count. X-rays of the joints of hands and/or feet were available from 47 patients.

Autoantibodies

Autoantibody profiles of IIM patients were determined during routine diagnostic workup using indirect immunofluorescence to screen for antinuclear antibodies (ANA) and anti-dsDNA (Immuno Concepts, Sacramento, USA), line immuno assay (Imtec Human, Wiesbaden, Germany) and myositis-westernblot (Euroimmun, Lübeck, Germany) for detection of individual autoantibodies directed against Jo-1, Mi-2, Ku, PM-Scl, PM-Scl75, PM-Scl100, PL-7, PL-12, EJ, OJ, SRP, Ro, Ro52, La, Scl-70, and U1-RNP antigens. In-house made ³⁵S radioimmunoprecipitation (21) was used to confirm the results and to detect autoantibodies not captured using commercial assays (against: TIF-1γ, MDA5, NXP2, Zo, EIF, RNAP I, RNAP II, and RNAP III). Rheumatoid factors (RF) were detected using a particle-agglutination assay (Fujirebio Inc., Tokyo, Japan); and an ELISA test for anti-CCP (Test – Line Clinical Diagnostics, Brno, Czech Republic) was used to detect antibodies against anti-citrullinated peptides (ACPA).

HLA typing

Allelic polymorphism of HLA-DRB1 and HLA-DQB1 genes was analyzed by DNA based typing using commercial sets (OneLambda, Los Angeles, USA) according to manufacturer's instructions.

Statistics

Demographics, clinical characteristics, and results are presented as descriptive statistics. The continuous not-normally distributed variables were analyzed by Mann-Whitney test; categorical data were analyzed by Fisher's exact test having p-values estimated by Monte Carlo simulations (N=10000), and Kaplan-Meier estimator was used for calculation of survival analysis of arthritis. The significance of the differences in allele and gene frequencies were evaluated by Fisher's exact test. We used GraphPad Prism 5 (GraphPad Software, La Jolla, California), QuickCalcs online calculator (graphpad.com), and R (r-project.org) for statistical analyses. P values <0.05 were considered to be statistically significant.

RESULTS

Demographic and clinical data of patients

In total, 106 patients with idiopathic inflammatory myopathies were included in the study. Basic demographic and clinical characteristics are summarized in Table 1.

Prevalence and characteristics of joint involvement

Combination of patients' medical history and cross-sectional physical examination revealed that arthritis at any time during the disease course had occurred in 56 (52.8%) patients (Table 2). Thirty nine patients (36.8%) had arthritis at the disease onset.

Thirty one patients (29.2%) presented with at least one swollen joint at the time of cross-sectional evaluation. Nine additional patients had only joint tenderness, with no swelling.

We did not find any difference in the prevalence of arthritis among individual IIM subgroups.

Probability of arthritis development

Patients with arthritis had significantly longer disease duration than those without arthritis ($p=0.04$) (Table 1). Patients who did not have arthritis at disease onset have a 65.6% (95% CI 57.1; 75.2) overall probability of its future development and this probability is gradually decreasing down to 33.9% (95% CI 23.6; 48.7) after ten years of arthritis-free survival (Figure 1). Thus, the probability of suffering from arthritis increases with the disease duration up to 66.1% (95% CI 51.3; 76.4) after 10 years.

Arthritis at the disease onset

Out of the 39 patients who had arthritis at the onset of IIM, joint symptoms preceded muscle weakness in 23 patients (59%), and occurred simultaneously in 16 (41%). Arthritis most commonly manifested as symmetrical polyarthritis in 33 cases (84.6%); oligoarthritis (involvement of 2-4 joints) and monoarthritis occurred in 5 (12.8%) and in one (2.6%) patient respectively.

Current arthritis at the time of evaluation

Out of the thirty one patients (29.2%) presenting with at least one swollen joint at the cross-sectional evaluation, five, 14 and 12 patients had one, 2-4, and more than four swollen joints, respectively. One patient had newly diagnosed swollen joint at this examination for the first time.

Mean affected/tender/swollen joint counts in patients with arthritis were 8.3 ± 9.1 ; 8.4 ± 9.4 and 5.3 ± 5.4 . Metacarpophalangeal (MCP), proximal interphalangeal joints of the fingers and thumbs (PIP/IP), wrists and shoulders were the most frequently involved joints (Table 3).

Other forms of joint involvement

Deforming arthropathy was present in 15 (14.2%) patients. Extreme lateral instability of the first interphalangeal joint (“floppy thumb”) occurred in five patients (4.7 %), four of them had anti-Jo-1 positive PM and one had anti-Mi-2 positive DM. Deformity in the first MCP was present in 3 patients (2.8%). All other deformities affected separate individual joints. Five patients (4.7%) had more than one joint deformity.

Radiographic characteristics of joint involvement

X-rays of peripheral joints were available in 47 patients. Forty-six and 37 patients had X-rays of the hands and feet, respectively. Out of the 15 patients with clinically apparent deforming arthropathy radiographs were available in 9 (60%). Joint erosions were present in two patients only: destructive arthritis of carpal joints in a patient with an overlap of PM with rheumatoid arthritis with a positivity of rheumatoid factor and anti-CCP autoantibodies; and destructive arthritis of the second and third metatarsophalangeal joints in one anti-Jo-1 positive DM patient.

Clinical aspects of IIM patients with arthritis

Disease relapses and arthritis

Myositis relapsed in 31 patients (29.2%) at any time during the course of the illness. Arthritis was a feature of the relapse in 15 patients (48.4%) and occurred most frequently concurrently with the myositis flare (8 cases; 53.3%) or shortly before or after the relapse of other myositis symptoms in 4 and 2 patients respectively; temporal pattern was not specified in one patient. The most common

manifestation of arthritis during IIM relapses was polyarthritis or oligoarthritis in 7 and 6 patients respectively (46.7 and 40%); detailed data on the number of affected joints were not available in two individuals.

Arthritis was present at disease onset in 13 out of 31 (41.9%) patients who later relapsed and in 29 out of 75 (38.7%) who did not. Thus, the presence of arthritis at the early phase of the disease is not predictive of future myositis relapses ($p=0.8$). Similarly, the presence of arthritis at disease onset does not predict whether the relapse will be associated with arthritis or not ($p=0.16$).

Clinical relevance of arthritis

Arthritis activity and joint damage was assessed using a Visual Analogue Scale by both patient and by the evaluating physician. The mean arthritis activity and joint damage scores were relatively low in the whole group due to a significant proportion of unaffected individuals. However, in patients with joint involvement, both mean activity of arthritis and joint damage were considered to be moderate (Table 4). Joint disease activity was rated higher by patients than by physicians ($p=0.01$). When joint disease was considered as a proportion of total morbidity on a semi-quantitative scale, 66 patients (62.3%) felt that arthritis did not play any role in the disease burden. Contribution of arthritis to the overall morbidity was reported to be small by 24 (22.6%), medium by 9 (8.5%) and large by 7 (6.6%) patients.

Autoantibodies

Myositis specific and myositis associated autoantibodies were tested in all patients and most patients were also evaluated for the presence of additional autoantibodies associated with other rheumatic diseases with frequent joint involvement (i.e. rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, and systemic sclerosis). Autoantibodies were found in 87 patients (82.1%). Not surprisingly, a strong association of anti-Jo-1 antibodies with arthritis was confirmed, with 27 out of 29 anti-Jo-1 positive patients (93%) having arthritis at some point during the course of IIM. The incidence of arthritis among anti-Jo1 positive patients was significantly higher compared to the anti-Jo-1 negative subjects ($p<0.0001$). No significant association between arthritis and autoantibody

positivity could be found for ANA (positive in 42.6% of tested patients), rheumatoid factors (10.2%), anti-Ro52 (32.7%), anti-Ro (11.5%), anti-PM-Scl (12.3%), anti-Mi-2 (6.7%), and anti-TIF-1 γ (8.2%). Other autoantibodies were found in very low frequencies and could not be statistically evaluated. Seven of nine RF positive patients and both patients with ACPA had arthritis. ACPA were positive at relatively high levels (patient Nr. 2: 239 U/l, patient Nr. 99: 114 U/l). Only patient number 2 fulfilled the 1987 ACR classification criteria for rheumatoid arthritis and was classified with an overlap syndrome.

Arthritis and HLA status

Allelic polymorphism of HLA-DRB1 and -DQB1 genes was analyzed in 71 and 73 patients and 179 and 175 healthy controls respectively. Patients had higher frequencies of HLA-DRB1*03 (56%) and HLA-DQB1*02 (70%) alleles in comparison with the control group (25% and 42%; $p < 0.0001$), but no evidence of an association between arthritis and these or any other HLA-DRB1 or -DQB1 alleles was observed (from $p = 0.2205$ to $p = 1.0000$).

DISCUSSION

We present anamnestic as well as cross-sectional data regarding joint involvement in a cohort of 106 consecutive patients with idiopathic inflammatory myopathies seen between January and September 2012 in a single center. To our knowledge our study represents the largest comprehensive overview of arthritis in an unselected cohort of IIM patients. The results show that arthritis is a common feature of myositis, affecting more than half of patients overall. Individual subtype of IIM most likely does not play a role in prevalence of arthritis. In the majority of patients with arthritis it manifests already at the onset of IIM, preceding symptoms of muscle weakness in half and appearing simultaneously in another one third. Survival analysis shows that the highest probability of future development of arthritis is at the beginning of the muscle disease, gradually decreasing for up to ten years of disease duration, with a significant residual risk even after this time period (Figure 1). This is supported by the fact that patients with arthritis had longer mean disease durations. We may hypothesize that joint

tenderness, without swelling, found in 9 patients at the cross-sectional examination might represent the first sign of newly developing arthritis in these patients.

Arthritis is also a common feature of disease relapses being present in about half of relapsing patients, most frequently occurring at the same time as the muscle symptoms. However, arthritis at the myositis onset is not predictive of the presence of arthritis during myositis relapses or of any future relapses of IIM.

Most frequently involved joints are shoulders and small joints of the hands – wrists, metacarpophalangeal and proximal interphalangeal joints, each affecting about one fifth of the patients, followed by elbows, ankles, and tarsal and acromioclavicular joints. The involvement of hand joints mimicking the distribution of involvement in rheumatoid arthritis (RA) together with the fact that arthritis often precedes the onset of muscle weakness may contribute to an occasional misdiagnosis of IIM as RA (22).

We have combined data obtained both in retrospective and cross sectional fashion; therefore we were not able to use a uniform definition of inflammatory arthritis. For the purpose of retrospective analysis, arthritis was defined as either an inflammatory arthritis diagnosed by a rheumatologist in the past and documented as such in the medical records or as a presence of both joint swelling and pain reported by the patient during the interview. Every attempt was done to confirm the inflammatory nature of the joint involvement and to rule out symptoms that could have been caused by osteoarthritis. For this reason a more stringent definition of arthritis requiring a simultaneous presence of both joint swelling and pain was applied. We are aware that, despite our efforts, retrospectively collected data might have caused arthritis overestimation. However, relying on medical records only would miss many arthritis cases, because especially mild and transitory forms of arthritis could have gone unreported.

Almost 30% of patients with IIM in our cohort had clinically apparent arthritis, defined as a presence of at least one swollen joint, at the time of cross-sectional evaluation. Polyarthritis was the most

frequent manifestation with a mean of five affected joints. This suggests that, when specifically looked for, arthritis is a frequent manifestation of IIM.

In our cohort, a strong association of arthritis with the presence of the anti-Jo-1 autoantibody was confirmed. The prevalence of arthritis among anti-Jo-1 positive patients was over 93%, which is more than was reported in some other studies (14, 23). The distribution of affected joints in our anti-Jo-1 positive patients was similar to previous reports and confirms a close relationship of joint disease with anti-Jo-1 antibodies. We could not demonstrate an association of arthritis with the presence of any other autoantibody, presumably due to the low numbers of patients in other autoantibody subgroups. Indeed, an association of arthritis with two other antisynthetase antibodies, anti-PL-7 (16) and anti-PL-12 (24), have been recently described. In these studies, unlike in our cohort, patients were included on the basis of autoantibody positivity rather than the diagnosis of IIM, therefore introducing a selection bias. Seven of nine RF positive patients and both patients with ACPA had arthritis. Only one of these patients fulfilled the 1987 ACR classification criteria for rheumatoid arthritis. These findings are in contrast with reports (25, 26) describing a relatively frequent overlap of IIM with RA, but are consistent with the original study of Bohan, who observed this combination more rarely in 2.3% of patients (27), and also with other reports (28). It may be clinically difficult to distinguish between arthritis as a manifestation of myositis and as a main clinical feature in RA, but the rare presence of typical deformities and X-ray erosions in those with available radiographs, argues against the frequent existence of the overlap syndrome.

Association of HLA-DRB1 or HLA-DQB1 polymorphism with arthritis was not found. As expected, we observed a higher frequency of HLA-DRB1*03 in our cohort. This allele has been associated with anti-Jo-1 antibodies (29), but it may be present also in patients with some other autoantibodies or without them. The absence of the association of HLA-DRB1*03 and arthritis in our patients suggests that rather the presence of anti-Jo-1 than HLA-DRB1*03 is the contributing factor.

Arthritis and joint involvement do not seem to significantly contribute to the overall disease burden in most IIM patients. The activity of arthritis was generally considered to be low to moderate by both

patients and physicians. Most patients assessed the contribution of arthritis to the overall morbidity to be none or only mild. It gives an impression that many patients perceive arthritis as less bothersome than other manifestations of myositis. However, in some patients arthritis contributes significantly to the overall morbidity. Seven patients judged the contribution of arthritis to be of large significance and in two cases the total morbidity was driven mostly by joint involvement. Moreover, nearly one half of the IIM relapses were associated with arthritis. Therefore, in some patients arthritis may be the main complaint and the choice of drug therapy should reflect this. However, since it is not known what treatment is best for arthritis in myositis, the same drugs used to treat other IIM manifestations are usually prescribed.

Arthritis in IIM is rarely deforming or erosive. In our cohort deforming arthropathy was present in 15% of patients and radiographic erosions were detected in two patients only (one overlap syndrome with RA and one with anti-Jo-1 positive DM); both these patients had clinically apparent deformities. These findings may be limited by the fact that not all of our patients had X-rays performed. However, since the X-rays were indicated based on the presence and severity of joint involvement, it is likely that most, if not all, patients with radiographic changes were captured. Five of our patients had so called floppy-thumb deformity (30), four of them (80%) were positive for anti-Jo-1 autoantibody, thus confirming previous report on this type of subluxing arthropathy (14).

In summary, we have documented that arthritis is a common, although usually not severe, feature of idiopathic inflammatory myopathies. It is often present at the beginning of the disease, even preceding the onset of muscle weakness in a substantial proportion of patients. Distribution of the most frequently involved joints is similar to that seen in rheumatoid arthritis. In our group, arthritis was mostly not deforming, although we found some previously described characteristic deformities in some patients.

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Table 1. Demographic and basic clinical data.

Patients, <i>n</i>	106
Gender; male/female	32/74
Age (years)	
Mean \pm SD	55.6 \pm 14.1
Median [95% CI]	59 [52.8; 58.3]
Diagnosis ^a	PM=46 [†] (43.4%) definite/probable/possible 26/11/9 DM=40 ^{§‡} (37.7%) definite/probable/possible 35/3/2 CAM=8 (7.5%) IMNM=11 (7.5%) IBM=1 (0.9%)
Disease duration (years) ^b	
Whole group	6.1 \pm 6.3 (4.4 [4.9;7.3])
Arthritis patients	6.8 \pm 5.7 (5.0 [5.3; 8.3]) [*]
Non-arthritis patients	5.3 \pm 6.8 (3.0 [3.3; 7.2]) [*]
Lung involvement	37 (34.9%)
Ever smokers	40 (37.7%)

PM – polymyositis; DM – dermatomyositis; CAM – cancer associated myositis; IMNM – immune mediated necrotizing myopathy; IBM – inclusion body myositis.

^a Muscle biopsy evaluable according to the ENMC criteria was available in 76 patients: 25 patients satisfied biopsy criteria for PM, 28 for DM, 11 for IMNM, 1 for IBM; nine biopsies did not have typical changes, and 2 were non-classifiable, with significant pathologies, but not consistent with a single diagnostic category (1).

[†] Including 5 patients with overlap syndromes: 3 scleroderma, 1 Sjögren’s syndrome, and 1 rheumatoid arthritis.

[§] Including 1 patient with clinically amyopathic dermatomyositis.

[‡] Including 3 patients with overlap syndromes: 2 scleroderma and 1 Sjögren’s syndrome.

^b Shown as mean \pm SD (median [95% CI]).

^{*} A significance difference was found between disease duration in arthritis and non-arthritis patients (p=0.04).

Table 2. Arthritis in myositis subtypes.

Diagnosis	Arthritis at any time	Arthritis at disease onset	Current arthritis (≥ 1 swollen joint)
PM (46)	27 (59%)	19 (41%)	17 (40%)
DM (40)	22 (55%)	15 (38%)	11 (28%)
CAM (8)	2 (25%)	1 (13%)	0 (0%)
IMNM (11)	4 (36%)	1 (13%)	2 (18%)
IBM (1)	1 (100%)	1 (100%)	1 (100%)
Total (106)	56 (53%)	39 (37%)	31 (29%)

PM – polymyositis; DM – dermatomyositis; CAM – cancer associated myositis; IMNM – immune mediated necrotizing myopathy; IBM – inclusion body myositis.

Arthritis at disease onset – based on patients' history. Current arthritis – arthritis present at the time of evaluation.

Arthritis at any time – combination of patients' history and clinical examination.

Table 3. Distribution of arthritis at the time of examination.

Joint	Number of patients with affected joints (%)		
	Tender	Swollen	Tender and/or swollen
Temporomandibular	7 (6.6%)	1 (0.9%)	7 (6.6%)
Sternoclavicular	7 (6.6%)	2 (1.9%)	7 (6.6%)
Acromioclavicular	13 (12.3%)	0	13 (12.3%)
Shoulder	22 (20.8%)	0	22 (20.8%)
Elbow	14 (13.2%)	5 (4.7%)	14 (13.2%)
Wrist	20 (18.9%)	11 (10.4%)	23 (21.7%)
Metacarpophalangeal I-V	18 (16.9%)	12 (11.3%)	22 (20.8%)
Proximal interphalangeal I-V	20 (18.9%)	20 (18.9%)	22 (20.8%)
Distal interphalangeal II-V	6 (5.7%)	5 (4.7%)	7 (6.6%)
Hip	4 (3.8%)	-	4 (3.8%)
Knee	9 (8.5%)	3 (2.8%)	10 (9.4%)
Ankle	12 (11.3%)	6 (5.7%)	13 (12.3%)
Tarsal joint	11 (10.4%)	3 (2.8%)	13 (12.3%)
Metatarsophalangeal I-V	11 (10.4%)	1 (0.9%)	11 (10.4%)
Interphalangeal I-V	2 (1.9%)	0	2 (1.9%)
Patients with at least one joint affected	45 (42.5%)	31 (29.2%)	52 (49%)

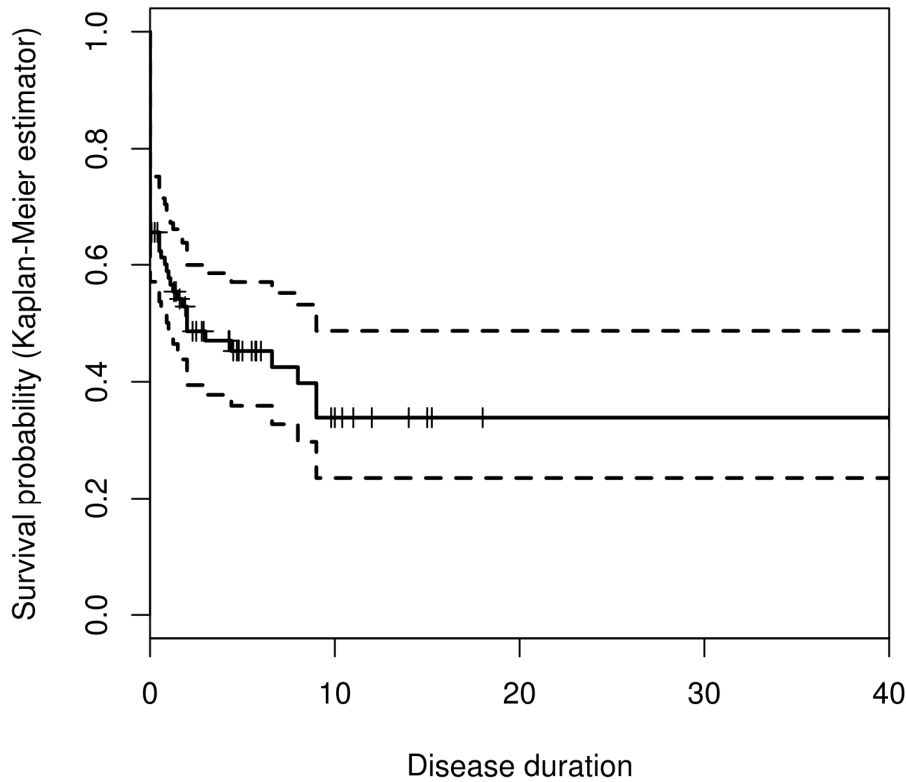
Table 4. Arthritis activity and damage.

	All patients	Patients with VAS>0
MD Activity	7.5±15.8	19.4±20.5 (<i>n</i> =41)
MD Damage	6.2±15.6	21.2±22.8 (<i>n</i> =31)
Pt Activity	14.0±21.5	26.5±23.4 (<i>n</i> =56)

MD/Pt – Physician's/Patient's assessment of activity/damage on Visual Analogue Scale (100 mm).

Data shown as mean±SD, (*n*)

Figure 1. Probability of survival without arthritis.



Probability of future development of arthritis in patients with arthritis-free survival (solid line) with 95% Confidential Intervals (dashed lines).
Crosses (+) indicate censoring.

Arthritis in idiopathic inflammatory myopathy: clinical features and autoantibody associations

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Peter Novota, Jiří Vencovský

ABSTRACT

Objectives. To determine the prevalence, distribution and clinical manifestations of arthritis in a cohort of patients with idiopathic inflammatory myopathies (IIM). Associations with autoantibody status and HLA genetic background were also explored.

Methods. One hundred and six consecutive patients with IIM treated in a single center were included in this cross-sectional study. History of arthritis, 68/66- tender and swollen joint index, clinical features of IIM, and autoantibody profiles were obtained by clinical examination, personal interview and review of patient's records. High resolution genotyping in HLA-DRB1 and HLA-DQB1 loci was performed in 71 and 73 patients respectively.

Results. Combination of patients' medical history and cross-sectional physical examination revealed that arthritis at any time during the disease course had occurred in 56 patients (53%). It was present at the beginning of the disease in 39 patients (37%) including 23 cases (22%) with arthritis preceding the onset of muscle weakness. On physical examination 29% of patients had at least one swollen ~~and 49% had at least one tender and/or swollen~~ joint. The most frequently affected areas were wrists, metacarpophalangeal and proximal interphalangeal joints. Twenty-seven out of the 29 anti-Jo-1 positive patients had arthritis at any time during the course of their illness; prevalence significantly higher compared to patients without the anti-Jo-1 autoantibody ($p < 0.0001$). No association of arthritis with individual HLA alleles was found.

Conclusions. Our data suggest that arthritis is a common feature of myositis. It is frequently present at the onset of disease and it may even precede muscular manifestations of IIM. Most common presentation is a symmetrical, non-erosive polyarthritis affecting particularly wrists, shoulders, and small joints of the hands. We have confirmed a strong association of arthritis with the presence of anti-Jo-1 antibody.

Key words: Idiopathic inflammatory myopathies, Arthritis, Autoantibodies

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Conclusions. Our data suggest that arthritis is a common feature of myositis. It is frequently present at the onset of disease and it may even precede muscular manifestations of IIM. Most common presentation is a symmetrical, non-erosive polyarthritis affecting particularly wrists, shoulders, and small joints of the hands. We have confirmed a strong association of arthritis with the presence of anti-Jo-1 antibody.

INTRODUCTION:

Idiopathic inflammatory myopathies (IIM) represent a group of systemic autoimmune disorders characterized by a non-suppurative inflammation of skeletal muscles as the major manifestation. Distinct subgroups of IIMs with variable clinical and laboratory manifestations are recognized, such as polymyositis (PM), dermatomyositis (DM), juvenile dermatomyositis (JDM), cancer-associated myositis (CAM), immune-mediated necrotizing myopathy (IMNM) and inclusion body myositis (IBM).

Arthritis is commonly seen in patients with IIM, however comprehensive data on its presentation and on manifestations in individual myositis subgroups is scarce (1). Arthritis is particularly frequent in patients with autoantibodies directed against tRNA synthetases as part of the antisynthetase syndrome (2-6), but it is not limited to this subgroup (7, 8). Arthritis and/or arthralgias were reported in 33% of IIM patients in a large multicenter Japanese cohort used for a formulation of new classification criteria, in which arthritis was included (9). Other available information originate from case reports (10-13) or small cohorts selectively defined by the presence of a specific autoantibody or anti-synthetase syndrome (5, 14-16). Arthritis in IIM patients is considered to be less severe and less destructive when compared to the joint involvement in rheumatoid arthritis, but the few available reports provide conflicting results in this aspect (5, 9-16). The degree of reported joint involvement in myositis varies from non-erosive arthritis (12) and subluxing arthropathy (5) to erosive and destructive arthritis (10, 13, 14).

The aim of this study was to provide comprehensive data regarding joint involvement in unselected patients with IIM from a single center. Specifically we determined the prevalence of arthritis in IIM patients; its relation to the course of the muscle disease; characteristics of arthritis with respect to distribution and extent as well as its association with autoantibody profiles and HLA allelic polymorphisms.

METHODS

Patients and Controls

All patients with IIM fulfilling diagnostic criteria seen both at the out- and in-patient departments of the Institute of Rheumatology between January to September 2012 were recruited into the study. The diagnosis of PM and DM was based on the criteria of Bohan and Peter (17, 18), necrotizing myopathy and amyopathic DM were diagnosed using the ENMC criteria (19); and the diagnosis of IBM was established using the Griggs criteria (20). All patients had a muscle biopsy performed during the course of their disease; however, the full description of the findings required for classification according to the ENMC criteria was available for the 76 biopsies performed after 2004 only. Control group for the genetic substudy consisted of 179 healthy subjects. The study was approved by the Ethics committee at the Institute of Rheumatology and all patients signed an informed consent.

Clinical Data

Basic demographic and clinical data including the history of IIM onset, disease course, smoking history and presence of lung involvement (defined as a presence of active alveolitis or fibrotic changes on X-ray or high resolution CT scan; and/or diffusing capacity of the lung for carbon monoxide <70%) were obtained from all patients. Information regarding presence or absence of arthritis in the past and/or at the current time with respect to the onset, localization, and symmetry as well as other features of joint involvement, such as presence of joint deformities, “floppy thumb” was obtained during personal interviews with patients and/or from medical records. Activity of arthritis and the degree of joint involvement were assessed by both patients and physicians using visual analogue scales (VAS). A semi-quantitative scale was used to evaluate the severity of joint involvement as a proportion of total morbidity. History of arthritis was established if the patient during personal interview reported having at least one painful and swollen joint in the past or if the presence of inflammatory arthritis detected by an experienced rheumatologist was recorded in the medical records. Current arthritis was defined as a presence of at least one swollen joint on physical examination using the 68/66-joint count. ~~The examination was performed by rheumatologists skilled in the detection of~~

~~arthritis; therefore we have also used a less stringent approach defining arthritis as a presence of at least one swollen and/or tender joint for secondary analysis.~~ X-rays of the joints of hands and/or feet were available from 47 patients.

Autoantibodies

Autoantibody profiles of IIM patients were determined during routine diagnostic workup using indirect immunofluorescence to screen for antinuclear antibodies (ANA) and anti-dsDNA (Immuno Concepts, Sacramento, USA), line immuno assay (Imtec Human, Wiesbaden, Germany) and myositis-westernblot (Euroimmun, Lübeck, Germany) for detection of individual autoantibodies directed against Jo-1, Mi-2, Ku, PM-Scl, PM-Scl75, PM-Scl100, PL-7, PL-12, EJ, OJ, SRP, Ro, Ro52, La, Scl-70, and U1-RNP antigens. In-house made ³⁵S radioimmunoprecipitation (21) was used to confirm the results and to detect autoantibodies not captured using commercial assays (against: TIF-1 γ , MDA5, NXP2, Zo, EIF, RNAP I, RNAP II, and RNAP III). Rheumatoid factors (RF) were detected using a particle-agglutination assay (Fujirebio Inc., Tokyo, Japan); and an ELISA test for anti-CCP (Test – Line Clinical Diagnostics, Brno, Czech Republic) was used to detect antibodies against anti-citrullinated peptides (ACPA).

HLA typing

Allelic polymorphism of HLA-DRB1 and HLA-DQB1 genes was analyzed by DNA based typing using commercial sets (OneLambda, Los Angeles, USA) according to manufacturer's instructions.

Statistics

Demographics, clinical characteristics, and results are presented as descriptive statistics. The continuous not-normally distributed variables were analyzed by Mann-Whitney test; categorical data were analyzed by Fisher's exact test having p-values estimated by Monte Carlo simulations (N=10000), and Kaplan-Meier estimator was used for calculation of survival analysis of arthritis. The significance of the differences in allele and gene frequencies were evaluated by Fisher's exact test. We used GraphPad Prism 5 (GraphPad Software, La Jolla, California), QuickCalcs online calculator

(graphpad.com), and R (r-project.org) for statistical analyses. P values <0.05 were considered to be statistically significant.

RESULTS

Demographic and clinical data of patients

In total, 106 patients with idiopathic inflammatory myopathies were included in the study. Basic demographic and clinical characteristics are summarized in Table 1.

Prevalence and characteristics of joint involvement

Combination of patients' medical history and cross-sectional physical examination revealed that arthritis at any time during the disease course had occurred in 56 (52.8%) patients (Table 2). ~~In a secondary analysis, which includes less stringent criteria for arthritis in cross-sectional examination, arthritis was demonstrated in 65 patients (61.3%).~~ Thirty nine patients (36.8%) had arthritis at the disease onset.

Thirty one patients (29.2%) presented with at least one swollen joint ~~and fifty-two patients (49%) had at least one swollen and/or tender joint(s)~~ at the time of cross-sectional evaluation. Nine additional patients had only joint tenderness, with no swelling.

We did not find any difference in the prevalence of arthritis among individual IIM subgroups, ~~irrespective of the definition of arthritis used. As a group, PM/DM patients had arthritis at any time significantly more often than IMNM/CAM patients (p=0.021) when less stringent criteria for arthritis were used, but not if only joint swelling was considered for definition of arthritis.~~

Probability of arthritis development

Patients with arthritis had significantly longer disease duration than those without arthritis (p=0.04) (Table 1). Patients who did not have arthritis at disease onset have a 65.6% (95% CI 57.1; 75.2) overall probability of its future development and this probability is gradually decreasing down to 33.9% (95% CI 23.6; 48.7) after ten years of arthritis-free survival (Figure 1). Thus, the probability of

suffering from arthritis increases with the disease duration up to 66.1% (95% CI 51.3; 76.4) after 10 years.

Arthritis at the disease onset

Out of the 39 patients who had arthritis at the onset of IIM, joint symptoms preceded muscle weakness in 23 patients (59%), and occurred simultaneously in 16 (41%). Arthritis most commonly manifested as symmetrical polyarthritis in 33 cases (84.6%); oligoarthritis (involvement of 2-4 joints) and monoarthritis occurred in 5 (12.8%) and in one (2.6%) patient respectively.

Current arthritis at the time of evaluation

Out of the thirty one patients (29.2%) presenting with at least one swollen joint at the cross-sectional evaluation, five, 14 and 12 patients had one, 2-4, and more than four swollen joints, respectively. One patient had newly diagnosed swollen joint at this examination for the first time.

~~Using the less stringent arthritis criteria requiring at least one tender and/or swollen joint, ten out of the 52 patients had newly detected arthritis during physical examination. Polyarthritis was detected in 24 (48.1%) patients, oligoarthritis and monoarthritis were present in 17 (32.7%) and 10 (19.2%) individuals respectively.~~

Mean affected/tender/swollen joint counts in patients with arthritis were 8.3 ± 9.1 ; 8.4 ± 9.4 and 5.3 ± 5.4 . Metacarpophalangeal (MCP), proximal interphalangeal joints of the fingers and thumbs (PIP/IP), wrists and shoulders were the most frequently involved joints (Table 3).

Other forms of joint involvement

Deforming arthropathy was present in 15 (14.2%) patients. Extreme lateral instability of the first interphalangeal joint ("floppy thumb") occurred in five patients (4.7 %), four of them had anti-Jo-1 positive PM and one had anti-Mi-2 positive DM. Deformity in of the first MCP was present in 3 patients (2.8%). All other deformities affected separate individual joints. Five patients (4.7%) had more than one joint deformity.

Radiographic characteristics of joint involvement

X-rays of peripheral joints were available in 47 patients. Forty-six and 37 patients had X-rays of the hands and feet, respectively. Out of the 15 patients with clinically apparent deforming arthropathy radiographs were available in 9 (60%). Joint erosions were present in two patients only: destructive arthritis of carpal joints in a patient with an overlap of PM with rheumatoid arthritis with a positivity of rheumatoid factor and anti-CCP autoantibodies; and destructive arthritis of the second and third metatarsophalangeal joints in one anti-Jo-1 positive DM patient.

Clinical aspects of IIM patients with arthritis

Disease relapses and arthritis

Myositis relapsed in 31 patients (29.2%) at any time during the course of the illness. Arthritis was a feature of the relapse in 15 patients (48.4%) and occurred most frequently concurrently with the myositis flare (8 cases; 53.3%) or shortly before or after the relapse of other myositis symptoms in 4 and 2 patients respectively; temporal pattern was not specified in one patient. The most common manifestation of arthritis during IIM relapses was polyarthritis or oligoarthritis in 7 and 6 patients respectively (46.7 and 40%); detailed data on the number of affected joints were not available in two individuals.

Arthritis was present at disease onset in 13 out of 31 (41.9%) patients who later relapsed and in 29 out of 75 (38.7%) who did not. Thus, the presence of arthritis at the early phase of the disease is not predictive of future myositis relapses ($p=0.8$). Similarly, the presence of arthritis at disease onset does not predict whether the relapse will be associated with arthritis or not ($p=0.16$).

Clinical relevance of arthritis

Arthritis activity and joint damage was assessed using a Visual Analogue Scale by both patient and by the evaluating physician. The mean arthritis activity and joint damage scores were relatively low in the whole group due to a significant proportion of unaffected individuals. However, in patients with joint involvement, both mean activity of arthritis and joint damage were considered to be moderate (Table

4). Joint disease activity was rated higher by patients than by physicians ($p=0.01$). When joint disease was considered as a proportion of total morbidity on a semi-quantitative scale, 66 patients (62.3%) felt that arthritis did not play any role in the disease burden. Contribution of arthritis to the overall morbidity was reported to be small by 24 (22.6%), medium by 9 (8.5%) and large by 7 (6.6%) patients.

Autoantibodies

Myositis specific and myositis associated autoantibodies were tested in all patients and most patients were also evaluated for the presence of additional autoantibodies associated with other rheumatic diseases with frequent joint involvement (i.e. rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, and systemic sclerosis). Autoantibodies were ~~detected~~found in 87 patients (82.1%). Not surprisingly, a strong association of anti-Jo-1 antibodies with arthritis was confirmed, with 27 out of 29 anti-Jo-1 positive patients (93%) having arthritis at some point during the course of IIM. The incidence of arthritis among anti-Jo1 positive patients was significantly higher compared to the anti-Jo-1 negative subjects ($p<0.0001$). No significant association between arthritis and autoantibody positivity could be found for ANA (positive in 42.6% of tested patients), rheumatoid factors (10.2%), anti-Ro52 (32.7%), anti-Ro (11.5%), anti-PM-Scl (12.3%), anti-Mi-2 (6.7%), and anti-TIF-1 γ (8.2%). Other autoantibodies were found in very low frequencies and could not be statistically evaluated. Seven of nine RF positive patients and both patients with ACPA had arthritis. ACPA were positive at relatively high levels (patient Nr. 2: 239 U/l, patient Nr. 99: 114 U/l). Only patient number 2 fulfilled the 1987 ACR classification criteria for rheumatoid arthritis and was classified with an overlap syndrome.

Arthritis and HLA status

Allelic polymorphism of HLA-DRB1 and -DQB1 genes was analyzed in 71 and 73 patients and 179 and 175 healthy controls respectively. Patients had higher frequencies of HLA-DRB1*03 (56%) and HLA-DQB1*02 (70%) alleles in comparison with the control group (25% and 42%; $p<0.0001$), but no

evidence of an association between arthritis and these or any other HLA-DRB1 or -DQB1 alleles was observed (from $p=0.2205$ to $p=1.0000$).

DISCUSSION

We present anamnestic as well as cross-sectional data regarding joint involvement in a cohort of 106 consecutive patients with idiopathic inflammatory myopathies seen between January and September 2012 in a single center. To our knowledge our study represents the largest comprehensive overview of arthritis in an unselected cohort of IIM patients. The results show that arthritis is a common feature of myositis, affecting more than half of patients overall. Individual subtype of IIM most likely does not

play a role in prevalence of arthritis. ~~however we observed arthritis being more frequently present in PM and DM in comparison with cancer associated myositis and immune mediated necrotizing myopathy when less stringent criteria for arthritis were applied.~~ In the majority of patients with

arthritis it manifests already at the onset of IIM, preceding symptoms of muscle weakness in half and appearing simultaneously in another one third. Survival analysis shows that the highest probability of future development of arthritis is at the beginning of the muscle disease, gradually decreasing for up to ten years of disease duration, with a significant residual risk even after this time period (Figure 1).

This is supported by the fact that patients with arthritis had longer mean disease durations. We may hypothesize that joint tenderness, without swelling, found in 9 patients at the cross-sectional examination may represent the first sign of a newly developing arthritis in these patients.

Arthritis is also a common feature of disease relapses being present in about half of relapsing patients, most frequently occurring at the same time as the muscle symptoms. However, arthritis at the myositis onset is not predictive of the presence of arthritis during myositis relapses or of any future relapses of IIM.

Most frequently involved joints are shoulders and small joints of the hands – wrists, metacarpophalangeal and proximal interphalangeal joints, each affecting about one fifth of the patients, followed by elbows, ankles, and tarsal and acromioclavicular joints. The involvement of hand joints mimicking the distribution of involvement in rheumatoid arthritis (RA) together with the fact

that arthritis often precedes the onset of muscle weakness may contribute to an occasional misdiagnosis of IIM as RA (22).

We have combined data obtained both in retrospective and cross sectional fashion; therefore we were not able to use a uniform definition of inflammatory arthritis. For the purpose of retrospective analysis, arthritis was defined as either an inflammatory arthritis diagnosed by a rheumatologist in the past and documented as such in the medical records or as a presence of both joint swelling and pain reported by the patient during the interview. Every attempt was done to confirm the inflammatory nature of the joint involvement and to rule out symptoms that could have been caused by osteoarthritis. For this reason a more stringent definition of arthritis requiring a simultaneous presence of both joint swelling and pain was applied. We are aware that, despite our efforts, retrospectively collected data might have caused arthritis overestimation. However, relying on medical records only would miss many arthritis cases, because especially mild and transitory forms of arthritis could have gone unreported.

Almost 30% of patients with IIM in our cohort had clinically apparent arthritis, defined as a presence of at least one swollen joint, at the time of cross-sectional evaluation. Polyarthritis was the most frequent manifestation with a mean of five affected joints. ~~In secondary analysis, in which a less stringent criterion of at least one tender and/or swollen joint was used, nearly one half of the patients presented with joint involvement.~~ This suggests that, when specifically looked for, arthritis is a frequent manifestation of IIM.

In our cohort, a strong association of arthritis with the presence of the anti-Jo-1 autoantibody was confirmed. The prevalence of arthritis among anti-Jo-1 positive patients was over 93%, which is more than was reported in some other studies (14, 23). The distribution of affected joints in our anti-Jo-1 positive patients was similar to previous reports and confirms a close relationship of joint disease with anti-Jo-1 antibodies. We could not demonstrate an association of arthritis with the presence of any other autoantibody, presumably due to the low numbers of patients in other autoantibody subgroups. Indeed, an association of arthritis with two other antisynthetase antibodies, anti-PL-7 (16) and anti-PL-12 (24), have been recently described. In these studies, unlike in our cohort, patients were included on the basis of autoantibody positivity rather than the diagnosis of IIM, therefore introducing a selection

bias. Seven of nine RF positive patients and both patients with ACPA had arthritis. Only one of these patients fulfilled the 1987 ACR classification criteria for rheumatoid arthritis. These findings are in contrast with reports (25, 26) describing a relatively frequent overlap of IIM with RA, but are consistent with the original study of Bohan, who observed this combination more rarely in 2.3% of patients (27), and also with other reports (28). It may be clinically difficult to distinguish between arthritis as a manifestation of myositis and as a main clinical feature in RA, but the rare presence of typical deformities and X-ray erosions in those with available radiographs, argues against the frequent existence of the overlap syndrome.

Association of HLA-DRB1 or HLA-DQB1 polymorphism with arthritis was not found. As expected, we observed a higher frequency of HLA-DRB1*03 in our cohort. This allele has been associated with anti-Jo-1 antibodies (29), but it may be present also in patients with some other autoantibodies or without them. The absence of the association of HLA-DRB1*03 and arthritis in our patients suggests that rather the presence of anti-Jo-1 than HLA-DRB1*03 is the contributing factor.

Arthritis and joint involvement do not seem to significantly contribute to the overall disease burden in most IIM patients. The activity of arthritis was generally considered to be low to moderate by both patients and physicians. Most patients assessed the contribution of arthritis to the overall morbidity to be none or only mild. It gives an impression that many patients perceive arthritis as less bothersome than other manifestations of myositis. However, in some patients arthritis contributes significantly to the overall morbidity. Seven patients judged the contribution of arthritis to be of large significance and in two cases the total morbidity was driven mostly by joint involvement. Moreover, nearly one half of the IIM relapses were associated with arthritis. Therefore, in some patients arthritis may be the main complaint and the choice of drug therapy should reflect this. However, since it is not known what treatment is best for arthritis in myositis, the same drugs used to treat other IIM manifestations are usually prescribed.

Arthritis in IIM is rarely deforming or erosive. In our cohort deforming arthropathy was present in 15% of patients and radiographic erosions were detected in two patients only (one overlap syndrome with RA and one with anti-Jo-1 positive DM); both these patients had clinically apparent deformities. These findings may be limited by the fact that not all of our patients had X-rays performed. However,

since the X-rays were indicated based on the presence and severity of joint involvement, it is likely that most, if not all, patients with radiographic changes were captured. Five our patients had so called floppy-thumb deformity (30), four of them (80%) were positive for anti-Jo-1 autoantibody, thus confirming previous report on this type of subluxing arthropathy (14).

In summary, we have documented that arthritis is a common, although usually not severe, feature of idiopathic inflammatory myopathies. It is often present at the beginning of the disease, even preceding the onset of muscle weakness in a substantial proportion of patients. Distribution of the most frequently involved joints is similar to that seen in rheumatoid arthritis. In our group, arthritis was mostly not deforming, although we found some previously described characteristic deformities in some patients.

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Table 1. Demographic and basic clinical data.

Patients, <i>n</i>	106
Gender; male/female	32/74
Age (years)	
Mean \pm SD	55.6 \pm 14.1
Median [95% CI]	59 [52.8; 58.3]
Diagnosis ^a	PM=46 [†] (43.4%) definite/probable/possible 26/11/9 DM=40 ^{§‡} (37.7%) definite/probable/possible 35/3/2 CAM=8 (7.5%) IMNM=11 (7.5%) IBM=1 (0.9%)
Disease duration (years) ^b	
Whole group	6.1 \pm 6.3 (4.4 [4.9;7.3])
Arthritis patients	6.8 \pm 5.7 (5.0 [5.3; 8.3]) [*]
Non-arthritis patients	5.3 \pm 6.8 (3.0 [3.3; 7.2]) [*]
Lung involvement	37 (34.9%)
Ever smokers	40 (37.7%)

PM – polymyositis; DM – dermatomyositis; CAM – cancer associated myositis; IMNM – immune mediated necrotizing myopathy; IBM – inclusion body myositis.

^a Muscle biopsy evaluable according to the ENMC criteria was available in 76 patients: 25 patients satisfied biopsy criteria for PM, 28 for DM, 11 for IMNM, 1 for IBM; nine biopsies did not have typical changes, and 2 were non-classifiable, with significant pathologies, but not consistent with a single diagnostic category (19).

[†] Including 5 patients with overlap syndromes: 3 scleroderma, 1 Sjögren’s syndrome, and 1 rheumatoid arthritis.

[§] Including 1 patient with clinically amyopathic dermatomyositis.

[‡] Including 3 patients with overlap syndromes: 2 scleroderma and 1 Sjögren’s syndrome.

^b Shown as mean \pm SD (median [95% CI]).

^{*} A significance difference was found between disease duration in arthritis and non-arthritis patients (p=0.04).

Table 2. Arthritis in myositis subtypes.

Diagnosis	Arthritis at any time	Arthritis at disease onset	Current arthritis (≥ 1 swollen joint)	Secondary analysis	
				Arthritis at any time	Current arthritis (≥ 1 swollen and/or tender) joint
PM (46)	27 (59%)	19 (41%)	17 (40%)	31 (67%)	25 (54%)
DM (40)	22 (55%)	15 (38%)	11 (28%)	26 (61%)	20 (50%)
CAM (8)	2 (25%)	1 (13%)	0 (0%)	2 (25%)	2 (25%)
IMNM (11)	4 (36%)	1 (13%)	2 (18%)	5 (45%)	4 (36%)
IBM (1)	1 (100%)	1 (100%)	1 (100%)	1 (100%)	1 (100%)
Total (106)	56 (53%)	39 (37%)	31 (29%)	65 (61%)	52 (49%)

PM – polymyositis; DM – dermatomyositis; CAM – cancer associated myositis; IMNM – immune mediated necrotizing myopathy; IBM – inclusion body myositis.

Arthritis at disease onset – based on patients' history. Current arthritis – arthritis present at the time of evaluation.

Arthritis at any time – combination of patients' history and clinical evaluation. ~~(swollen joints). In secondary analysis, combination of patients' history and clinical evaluation with less stringent criteria (tender and/or swollen) was used.~~

Table 3. Distribution of arthritis at the time of examination.

Joint	Number of patients with affected joints (%)		
	Tender	Swollen	Tender and/or swollen
Temporomandibular	7 (6.6%)	1 (0.9%)	7 (6.6%)
Sternoclavicular	7 (6.6%)	2 (1.9%)	7 (6.6%)
Acromioclavicular	13 (12.3%)	0	13 (12.3%)
Shoulder	22 (20.8%)	0	22 (20.8%)
Elbow	14 (13.2%)	5 (4.7%)	14 (13.2%)
Wrist	20 (18.9%)	11 (10.4%)	23 (21.7%)
Metacarpophalangeal I-V	18 (16.9%)	12 (11.3%)	22 (20.8%)
Proximal interphalangeal I-V	20 (18.9%)	20 (18.9%)	22 (20.8%)
Distal interphalangeal II-V	6 (5.7%)	5 (4.7%)	7 (6.6%)
Hip	4 (3.8%)	-	4 (3.8%)
Knee	9 (8.5%)	3 (2.8%)	10 (9.4%)
Ankle	12 (11.3%)	6 (5.7%)	13 (12.3%)
Tarsal joint	11 (10.4%)	3 (2.8%)	13 (12.3%)
Metatarsophalangeal I-V	11 (10.4%)	1 (0.9%)	11 (10.4%)
Interphalangeal I-V	2 (1.9%)	0	2 (1.9%)
Patients with at least one joint affected	45 (42.5%)	31 (29.2%)	52 (49%)

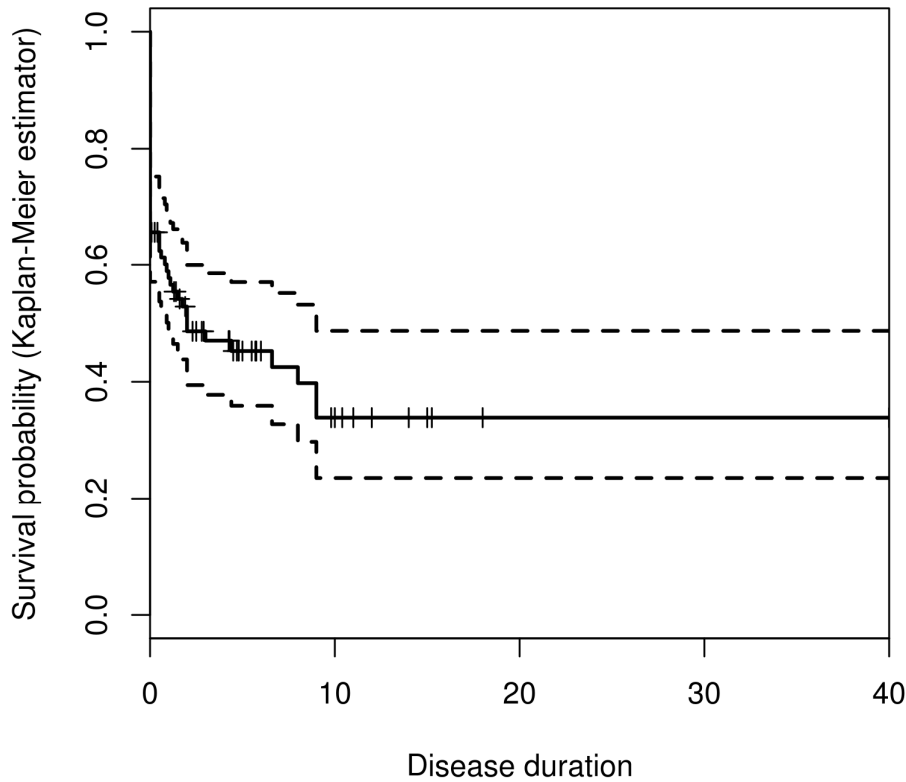
Table 4. Arthritis activity and damage.

	All patients	Patients with VAS>0
MD Activity	7.5±15.8	19.4±20.5 (<i>n</i> =41)
MD Damage	6.2±15.6	21.2±22.8 (<i>n</i> =31)
Pt Activity	14.0±21.5	26.5±23.4 (<i>n</i> =56)

MD/Pt – Physician's/Patient's assessment of activity/damage on Visual Analogue Scale (100 mm).

Data shown as mean±SD, (*n*)

Figure 1. Probability of survival without arthritis.



Probability of future development of arthritis in patients with arthritis-free survival (thicksolid line) with 95% Confidential Intervals (dashed lines).
Crosses (+) indicate censoring.